

—CHAPTER 5—

**COMPARATIVE NEUROPHARMACOLOGY
OF IBOGAINE AND ITS
O-DESMETHYL METABOLITE, NORIBOGAINE**

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I. Introduction.....

II. Pharmacokinetics.....

III. Neurochemical Mechanisms.....

 A. Effects on Dopamine Systems.....

 B. Effects on Serotonin Systems.....

 C. Effects on Opioid Systems.....

IV. Neuroendocrine Effects.....

V. Adverse Consequences.....

 A. Behavioral Effects.....

 B. Neurotoxicity.....

VI. Conclusions.....

 References.....

I. Introduction

Drug addiction is a disease that affects millions of people worldwide (1). The severity of the drug addiction problem, coupled with a lack of effective medications, has prompted investigators to explore the plant kingdom as a source of novel therapeutics. One example of a plant-derived compound with potential utility in treating drug addiction is the indole alkaloid, ibogaine (2,3). Ibogaine is found in the roots of the African shrub, *Tabernanthe iboga*. Historically, native peoples of West Central Africa have used the root bark of this plant as a sacrament in their rituals of initiation into adulthood (4). More recently, ibogaine has gained a reputation as an “addiction interrupter,” based on findings in animals and humans (reviewed in 5,6). In rats, acute administration of ibogaine (40 mg/kg, i.p.) produces long-lasting decreases in the self-administration of cocaine and morphine (7-9, see Glick *et al.* in this volume). Ibogaine also alleviates symptoms of opioid withdrawal in morphine-dependent rats (10,11) and heroin-dependent human addicts (12,13, see Alper *et al.* this volume). These promising findings support the development of ibogaine as a pharmacological adjunct in the treatment of substance use disorders.

Despite extensive investigation, the mechanisms underlying the antiaddictive properties of ibogaine are not fully understood (14,15). Radioligand binding studies show that ibogaine binds with low micromolar (μM) affinity to a number of molecular targets in nervous tissue, resulting in a complex pharmacology (16-27). Some of these ibogaine binding sites include sigma-2 receptors (16,17), serotonin (5-HT) and dopamine (DA) transporters (18-21), mu- and kappa-opioid receptors (21-24), and NMDA-coupled ion channels (25-27). Biodistribution studies in rats demonstrate that brain concentrations of ibogaine range from 10 to

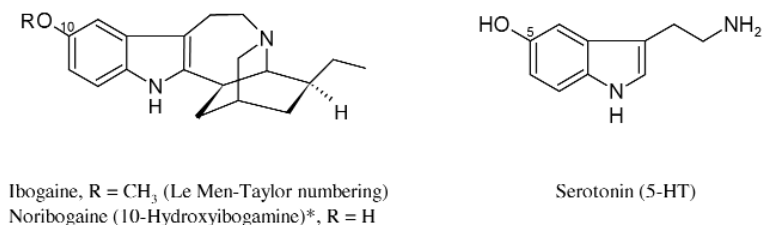


FIGURE 1. Chemical structures of ibogaine, its *O*-demethylated metabolite (noribogaine), and the neurotransmitter serotonin (5-HT).

* Noribogaine (10-hydroxyibogamine) has frequently been referred to as 12-hydroxyibogamine in the biological and medical literature based on the Chemical Abstracts numbering system for the ibogamine alkaloid skeleton.

20 μM when measured 1 hour after acute administration of 50 mg/kg p.o. (21) or 40 mg/kg i.p. (28,29). Thus, the interaction of ibogaine with μM -affinity binding sites may be functionally relevant *in vivo*. Few studies have been able to attribute *in vivo* pharmacological effects of ibogaine to activation of specific binding sites. In fact, there is speculation that the key to ibogaine's antiaddictive potential is related to the simultaneous activation of multiple neurotransmitter systems in the brain (14,15).

An intriguing aspect of ibogaine pharmacology is the long-lasting action of the drug. In rats, a single administration of ibogaine elicits behavioral and neurochemical effects that can last for days (7-9,18,30,31), even though the biological half-life of the drug is only a few hours (32,33). Such observations suggest the possibility that ibogaine is converted to a long-acting metabolite (7-9). Mash *et al.* (19) and Hearn *et al.* (34) provided the first direct evidence for the formation of a major ibogaine metabolite *in vivo*. These investigators used sensitive analytical methods to identify an *O*-demethylated metabolite of ibogaine, 10-hydroxyibogamine (noribogaine), in the blood and urine from monkeys and humans treated with ibogaine. Figure 1 shows the chemical structures of ibogaine, noribogaine, and the neurotransmitter serotonin (5-hydroxytryptamine, 5-HT). The methoxy group at the 10-position of ibogaine is converted to a hydroxyl group to form noribogaine. Note the presence of an indole moiety in the structure of the *iboga* alkaloids and 5-HT. Subsequent pharmacokinetic studies have demonstrated that ibogaine is converted to noribogaine in rats (21,29).

Interestingly, as summarized in Table I, the *in vitro* pharmacology of noribogaine differs significantly from that of ibogaine. For example, noribogaine displays a higher affinity for 5-HT transporters (SERTs) and opioid receptor subtypes when compared to ibogaine. A growing body of preclinical evidence demonstrates that noribogaine is biologically active *in vivo* and undoubtedly

TABLE I.
AFFINITIES OF IBOGAINE AND NORIBOGAINE AT SELECTED SITES

| Binding site (ref.) | Radioligand ^a | Ibogaine (K _i , μM) | Noribogaine (K _i , μM) |
|-----------------------------|-----------------------------|---|--|
| Sigma-2 receptors (16) | [³ H]-DTG | 0.20 | 5.26 |
| 5-HT transporters (19) | [¹²⁵ I]-RTI-55 | 0.55 | 0.04 |
| DA transporters (19) | [¹²⁵ I]-RTI-121 | 1.98 | 2.05 |
| Mu-opioid receptors (24) | [³ H]-DAMGO | 3.76 | 0.16 |
| Kappa-opioid receptors (23) | [³ H]-U69,593 | 3.77 | 0.96 |
| NMDA sites (21) | [³ H]-MK-801 | 5.20 | 31.41 |

^a Specific details of the radioligand binding assays and the calculation of inhibitory constants, K_i, are described in the cited references in parentheses.

contributes to the spectrum of effects produced by systemically administered ibogaine (19,35-41). The primary aim of this chapter is to review the comparative neurobiology of ibogaine and noribogaine in rodent species. The chapter focuses on data collected from the laboratories of the authors and attempts to integrate these findings with the available literature on *iboga* alkaloids.

II. Pharmacokinetics

Pharmacokinetic studies carried out in the early 1970s showed that systemic administration of ibogaine to rats and mice is followed by rapid distribution of the drug into various organs, including brain, liver, and kidney (32,33). The same studies determined the elimination kinetics of ibogaine from the brain and reported a half-life of about 1 hour. More recently, a number of laboratories have developed sensitive analytical methods to detect ibogaine in blood and other tissues (34, 42-44). These methods generally involve organic extraction of tissue samples, a derivatization procedure, and subsequent quantitation of ibogaine via gas chromatography-mass spectroscopy (GC/MS). Using these GC/MS methods, Hough *et al.* (28) examined the tissue distribution of ibogaine in rats after administration of i.p. or s.c. injections. One hour after an i.p. injection of ibogaine (40 mg/kg), tissue concentrations of the drug varied widely, ranging from 100 ng/ml in plasma to 10 µg/g in fat. These drug concentrations decreased nearly 10-fold by 12 hours postinjection. In all instances, tissue levels of ibogaine were greater after s.c. administration when compared to i.p. administration.

Findings from the work of Hough *et al.* indicate two possible mechanisms whereby ibogaine could have long-lasting actions *in vivo*. First, the high concentration of ibogaine in fat tissue suggests that fat can serve as a storage depot for the drug. Under these circumstances, it seems feasible that small amounts of ibogaine could be released from fat tissue into the circulation for extended periods after a single dose. Second, the lower tissue concentrations of ibogaine observed after i.p. administration suggest that ibogaine is extensively metabolized when given by the i.p. route.

As mentioned previously, Mash and coworkers (19,34) identified noribogaine as the major metabolite of ibogaine in monkeys and humans. These investigators postulated that noribogaine is formed via first-pass metabolism of ibogaine in the liver. In agreement with this notion, Obach *et al.* (45) reported that ibogaine is *O*-demethylated by cytochrome P450 enzymes in human liver microsomes *in vitro*. In particular, cytochrome P450 2D6 appears to be the main isoform responsible for ibogaine *O*-demethylase activity in humans. While noribogaine has been identified in plasma and brain tissue from rats treated with ibogaine (21,29,41),

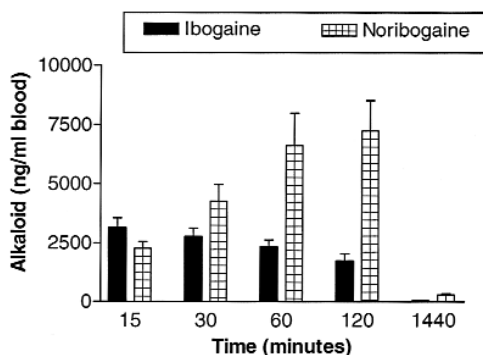


FIGURE 2. Time-concentration profiles for ibogaine and its *O*-demethylated metabolite, noribogaine, in rats. Male rats fitted with indwelling jugular catheters received i.p. ibogaine (40 mg/kg, i.p.) at time zero, and blood samples were drawn at various times thereafter. Whole blood levels of ibogaine and noribogaine were assayed using GC/MS. Data are mean \pm SEM for $N = 6$ /group.

no study has determined the specific cytochrome P450 isoform(s) responsible for formation of noribogaine in rats or other species.

In our laboratory, we have been interested in the pharmacokinetics and metabolism of ibogaine in rats, because this animal species is the principal model system used for evaluating the antiaddictive properties of ibogaine. With this in mind, we carried out investigations to examine the metabolic conversion of ibogaine to noribogaine in rats (46). Male rats were fitted with indwelling jugular catheters and allowed one week to recover. On the morning of an experiment, rats received an i.p. injection of ibogaine (40 mg/kg), and repeated blood samples were withdrawn via the catheters at various times thereafter for 24 hours. Whole blood samples were assayed for ibogaine and noribogaine using GC/MS methods (34).

Figure 2 shows that ibogaine is rapidly metabolized to noribogaine in rats, and the maximal blood concentration of noribogaine exceeds that of ibogaine by more than 2-fold. At 24 hours postinjection, blood levels of ibogaine are undetectable whereas blood levels of noribogaine are in the range of 300 ng/ml. Thus, noribogaine is present in the bloodstream at pharmacologically relevant concentrations for at least one day postinjection, long after ibogaine has been cleared. Biodistribution studies in rats have shown that noribogaine readily penetrates the blood-brain barrier and enters into the brain (21,29,41). In fact, brain concentrations of noribogaine are equal to, or greater than, brain concentrations of ibogaine after i.p. or oral administration of ibogaine (21,29,41). These data clearly show that noribogaine can contribute to the acute and long-lasting effects of ibogaine administered systemically in rats.

It should be mentioned that the concentrations of ibogaine and noribogaine in rat blood shown in Figure 2 are much higher than the concentrations of these alkaloids in rat plasma reported by others (28,29). This observation suggests that ibogaine and noribogaine are sequestered in some cellular fraction of whole blood. One possibility is that *iboga* alkaloids are taken up into blood platelets by a process involving SERT sites present on platelet cell membranes. While this hypothesis is speculative, Table I shows that both ibogaine and noribogaine have significant affinity for SERT. The nature of the interaction between *iboga* alkaloids and platelet SERTs has not been well characterized and deserves to be studied.

Pearl *et al.* (29) have reported gender differences in responsiveness to ibogaine, with females exhibiting a greater sensitivity to the effects of the drug. These investigators also showed that female rats have significantly higher levels of ibogaine and noribogaine in brain tissue after i.p. administration of ibogaine. Thus, the enhanced ibogaine sensitivity in females may be due to pharmacokinetic differences between sexes. In order to further assess the role of gender and gonadal steroids on the kinetics and metabolism of ibogaine, we carried out an investigation using groups of male and female rats with differing sex hormone status (47). Five groups of rats were used: (1) intact sham-operated males, (2) castrated males, (3) intact females prior to ovulation (i.e. in proestrus phase), (4) intact females after ovulation (i.e., in diestrus phase), and (5) ovariectomized females. All rats were fitted with indwelling jugular catheters at the time of sham surgery or gonadectomy, and allowed one week to recover. In the intact female groups, vaginal cytology was monitored to track the stage of the estrous cycle. Preovulatory females were subjected to experimental testing during the proestrus stage of the cycle, when circulating levels of endogenous estrogen are high. Postovulatory females were tested the day after the estrus stage of the cycle when levels of estrogen are lower. On the day of an experiment, rats received 40 mg/kg i.p. ibogaine, and repeated blood samples were withdrawn via the catheters at various times thereafter. Levels of *iboga* alkaloids in whole blood were assayed by GC/MS.

Table II summarizes the effects of gender and gonadectomy on blood levels of ibogaine and noribogaine after i.p. ibogaine injection. In all groups, ibogaine concentrations in blood reach maximum within 10 to 12 minutes, whereas noribogaine concentrations reach maximum between 1 and 3 hours postinjection. Importantly, preovulatory females with high circulating estrogen display nearly 2-fold greater blood levels of ibogaine when compared to all other groups. This observation supports the findings of Pearl *et al.*, who showed female rats have higher plasma and brain levels of ibogaine when compared to male rats (29). Thus, it appears that estrogen increases the bioavailability of ibogaine, and this effect may be mediated by enhanced absorption of the drug from the peritoneal cavity into the circulation. In the castrated males and ovariectomized females,

TABLE II.
EFFECTS OF GENDER AND GONADECTOMY ON THE KINETICS AND
METABOLISM OF IBOGAINE AND NORIBOGAINE IN RATS

| Condition/ Gender | Ibogaïne AUC ^a (ng*h/ml) | Tmax (h) | Noribogaïne AUC (ng*h/ml) | Tmax (h) |
|-----------------------|---|---------------|---------------------------------|----------------|
| Control Male | 8350 ± 243 ^b | 0.167 ± 0.010 | 27181 ± 2102 | 0.834 ± 0.074 |
| Castrated Male | 7983 ± 496 | 0.195 ± 0.028 | 11631 ± 1003* | 1.667 ± 0.211* |
| Preovulatory Female | 15898 ± 939* | 0.195 ± 0.028 | 34811 ± 1948 | 3.000 ± 0.447* |
| Postovulatory Female | 8477 ± 396 | 0.167 ± 0.010 | 30960 ± 2246 | 2.780 ± 0.211* |
| Ovariectomized Female | 8933 ± 614 | 0.167 ± 0.010 | 15891 ± 1805* | 3.330 ± 0.667* |

^a Area under the curve (AUC) and time to achieve maximal drug concentration (Tmax) were calculated using PCNONLIN computer software.

^b Values are mean ± SEM for N = 6 rats/group.

* = P < 0.05 with respect to sham-operated control males.

noribogaïne concentrations are significantly lower than in the other groups. These data suggest that gonadectomy decreases the metabolic conversion of ibogaïne to noribogaïne. Taken together, the data demonstrate that the sex steroid modulation of ibogaïne kinetics and metabolism is complex. While elevations in estrogen can increase bioavailability of ibogaïne, removal of gonadal steroids impairs the metabolism of ibogaïne to noribogaïne. Such gender differences in ibogaïne pharmacokinetics have important implications. First, caution should be exercised when administering ibogaïne to female animals or humans because females will be more sensitive to the effects of the drug. Second, when interpreting data from studies using female rats, it must be remembered that pharmacological effects of ibogaïne may be greater in females as compared to males for the same dose of drug.

III. Neurochemical Mechanisms

A. EFFECTS ON DOPAMINE SYSTEMS

A large body of preclinical evidence shows that mesolimbic dopamine (DA) neurons are involved in drug-associated reward processes (48,49). The mesolimbic DA system in rodents consists of cell bodies residing in the ventral tegmental area (VTA) that send axonal projections to numerous limbic forebrain regions, most notably the nucleus accumbens (NAC) and prefrontal cortex (PFC). Acute administration of abused drugs, such as morphine and cocaine, causes

elevations in the concentration of extracellular DA in rat NAC (50,51). Withdrawal from chronic exposure to these abused drugs, in contrast, results in significant reductions in extracellular DA in the NAC (52,53). Thus, increased synaptic DA is associated with the positive rewarding effects of drugs (i.e., euphoria), whereas decreased synaptic DA is associated with negative withdrawal effects (i.e., dysphoria). Current theories of addiction suggest that both the positive and negative effects of drugs are involved in the maintenance of a drug-dependent state (54,55).

Because of the prominent role of DA in drug addiction, it seems conceivable that the antiaddictive properties of ibogaine might be related to effects of the drug on DA systems in the brain. Radioligand binding studies demonstrate that ibogaine does not interact with DA receptor subtypes *in vitro* (20-22), thus ibogaine is not a direct DA agonist or antagonist. A number of investigators have shown that ibogaine binds with low μM affinity to DA transporter proteins (DATs) labeled with the cocaine analogs [^3H]WIN-35,428 and [^{125}I]RTI-121 (18-21). In contrast, Broderick *et al.* (56) reported that concentrations of ibogaine up to 100 μM do not affect DAT binding when transporters are labeled with the piperazine analog [^3H]GBR12935. These apparently discordant results may be explained by the findings of Vaughan (57), who showed that cocaine-like drugs (i.e. phenyltropanes) and GBR-like drugs (i.e. phenylpiperazines) bind to different regions of the DAT polypeptide. It seems plausible that ibogaine exhibits selective affinity for a cocaine-binding domain located on DAT proteins.

DAT sites are important regulatory elements in the brain. Under normal circumstances, DATs function to recapture released DA from the synapse and transport it back into the intraneuronal cytoplasm (58,59). The DA uptake activity of DAT is the principal mechanism for inactivating DA transmission. Mash *et al.* (19, 21) demonstrated that ibogaine and noribogaine display low μM affinity for

TABLE III.
INHIBITORY POTENCY OF IBOGAINE AND NORIBOGAINE IN ASSAYS OF
TRANSPORTER BINDING AND MONOAMINE UPTAKE IN RAT BRAIN

| Assay ^a | Ibogaine IC ₅₀ (μM) | Noribogaine IC ₅₀ (μM) |
|--|--|---|
| [^{125}I]RTI-55-labeled DA transporters (DAT) | 11.83 \pm 0.39 ^b | 4.17 \pm 0.19 |
| [^{125}I]RTI-55-labeled 5-HT transporters (SERT) | 3.85 \pm 0.21 | 0.18 \pm 0.01 |
| [^3H]DA uptake rat caudate | 10.03 \pm 0.72 | 13.05 \pm 0.72 |
| [^3H]5-HT uptake rat whole brain minus cerebellum | 3.15 \pm 0.10 | 0.33 \pm 0.02 |

^aBinding assays used [^{125}I]RTI-55 to label DAT and SERT sites in rat caudate membranes. DAT binding was conducted in the presence of 50 nM paroxetine whereas SERT binding was conducted in the presence of 100 nM GBR12935. Uptake assays were performed in synaptosomes prepared from rat brain.

^bValues are mean \pm SD expressed as IC₅₀ values determined from three independent experiments each performed in triplicate.

DAT sites in human brain tissue (see Table I). In order to further explore the interactions of *iboga* alkaloids with DATs, the effects of ibogaine and noribogaine in assays measuring DAT binding and [³H]DA uptake in rat brain tissue preparations were tested. As depicted in Table III, ibogaine and noribogaine are low potency inhibitors of DAT binding when DAT sites are labeled with the cocaine analog [¹²⁵I]RTI-55. More importantly, both *iboga* alkaloids block the uptake of [³H]DA into rat caudate synaptosomes with IC₅₀ values in the range of 10 μM. These findings agree with the recent data of Wells *et al.* (60), who reported that ibogaine inhibits [³H]DA uptake in rat striatal synaptosomes with an IC₅₀ of 20 μM. These same investigators showed that ibogaine does not evoke appreciable release of preloaded [³H]DA from nervous tissue. It is noteworthy that ibogaine and noribogaine possess similar IC₅₀ values in assays measuring inhibition of DAT binding and inhibition of [³H]DA uptake; this indicates that the binding-to-uptake ratios for these alkaloids are close to one. We have previously reported that drugs exhibiting binding-to-uptake ratios close to unity are pure uptake blockers (61). According to this classification scheme, ibogaine and noribogaine are low-potency DA uptake inhibitors *in vitro*.

There are a number of research methods available for studying DA neurochemistry *in vitro* and *in vivo*. Sershen *et al.* have published an excellent review (62, see Sershen *et al.* in this volume) summarizing the use of *in vitro* perfusion techniques to assess the effects of ibogaine on [³H]DA release, so this topic will not be discussed further here. For whole animal studies, two basic neurochemical methods have been used to examine the effects of *iboga* alkaloids on DA function in rodents: (1) measurement of DA and its metabolites, dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), in tissue samples from postmortem brain, and (2) measurement of DA and its metabolites in extracellular fluid from living brain using *in vivo* microdialysis sampling. It is important to realize that these two methods assess different aspects of DA neuronal function. For example, the amount of DA in brain extracellular fluid is presumably an index of synaptic DA that is, in turn, dependent on the combined processes of DA cell firing, DA release, and DA reuptake. Additionally, the amount of DA in extracellular fluid is a very small fraction of the total content of DA in brain tissue. In the present discussion, the term "tissue DA" will be used to designate DA levels measured in postmortem brain tissue, whereas the term "dialysate DA" will be used to designate DA levels measured in microdialysis samples.

It is well established that ibogaine administration causes dramatic changes in the tissue levels of DA and its metabolites in rodent brain (18,30,31), and these changes are dose and time dependent. In our laboratory, the time-course effects of ibogaine on DA metabolism in rats were examined (31). Groups of male rats received 50 mg/kg i.p. ibogaine and were sacrificed at various times thereafter for up to 24 hours. Brain regions were dissected, and tissue levels of DA, DOPAC,

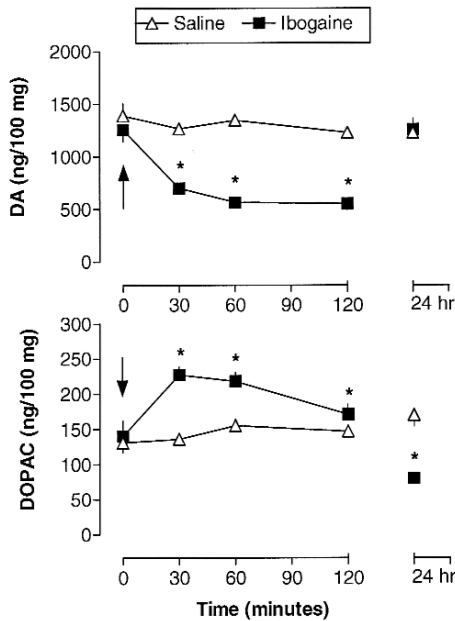


FIGURE 3. Time-course effects of ibogaine administration on postmortem tissue levels of DA and DOPAC in rat caudate. Rats received saline or ibogaine (50 mg/kg, i.p.) at time zero, and groups of rats (N = 6 per group at each time point) were sacrificed at various times thereafter. Tissue levels of DA and DOPAC were assayed using HPLC-EC.

* = $P < 0.05$ compared to saline control at specific time points (31).

and HVA were assayed by high-pressure liquid chromatography with electrochemical detection (HPLC-EC). Figure 3 illustrates the time-course effects of ibogaine on tissue DA and DOPAC in rat caudate. Ibogaine causes marked decreases (~50% reductions) in tissue DA levels that last for at least 2 hours. The acute reduction in tissue DA is accompanied by concomitant increases in tissue levels of DOPAC and HVA (30,31). By 24 hours postinjection, DA levels return to normal whereas metabolite levels are reduced significantly. The acute stimulation of DA utilization evoked by ibogaine, as indicated by increased DOPAC/DA ratios, has been observed in every rat brain region examined including, PFC, hypothalamus, olfactory tubercle, and NAC (30,31,63-66). Thus, ibogaine exerts a biphasic effect on DA utilization that is characterized by an initial transient increase in metabolism followed by a more persistent decrease.

Given the dramatic effects of ibogaine on DA metabolism, it is surprising that no studies have reported the effects of noribogaine on tissue levels of DA and its metabolites. To address this issue, the effects of ibogaine and noribogaine on DA

metabolism were compared in mice (65). Groups of male mice received ibogaine or noribogaine (30 or 100 mg/kg, i.p.) and were sacrificed at 60 minutes postinjection. Brain regions were dissected, and tissue levels of DA, DOPAC, and HVA were determined by HPLC-EC. Figure 4 depicts the effects of ibogaine and noribogaine on tissue DA and DOPAC in mouse caudate. Similar to the effects of ibogaine in rats, ibogaine and noribogaine produce dose-dependent reductions in tissue DA in mouse caudate. Additionally, both drugs cause a parallel increase in DOPAC over the same time course. Ibogaine and noribogaine are essentially equipotent in their ability to stimulate DA metabolism in mice, and this property of the *iboga* alkaloids appears similar between mice and rats.

The effects of ibogaine and noribogaine on extracellular DA levels have been investigated extensively. Maisonneuve *et al.* (67) published the first study examining the influence of ibogaine (40 mg/kg, i.p.) on dialysate DA in rat brain, and their findings showed that ibogaine alters DA levels in a region-specific manner. When examined 1 hour after ibogaine injection, dialysate DA levels are

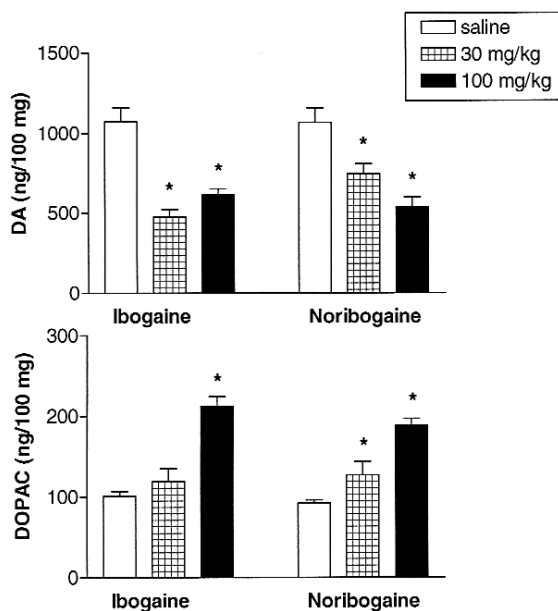


FIGURE 4. Dose-response effects of ibogaine and noribogaine on postmortem tissue levels of DA and DOPAC in mouse caudate. Groups of male mice ($N = 6$ per group at each dose) received saline, ibogaine, or noribogaine and were sacrificed 60 minutes later. Tissue levels of DA and DOPAC were determined using HPLC-EC.

* = $P < 0.05$ with respect to saline controls (65).

increased in the frontal cortex, decreased in the caudate, and unchanged in the NAC. Broderick *et al.* (68) used *in vivo* microvoltammetry to confirm that ibogaine (40 mg/kg, i.p.) does not significantly alter extracellular DA levels in the NAC of male rats. Similarly, Benwell *et al.* (66) observed that dialysate DA in rat NAC is unchanged after ibogaine treatment. We have examined the acute effects of i.v. ibogaine and noribogaine (1 and 10 mg/kg) on extracellular DA in the NAC of male rats, and our findings show that neither drug significantly affects dialysate DA (19,46). In apparent contrast to the above-mentioned results, Glick *et al.* (15,35) reported that systemic administration of ibogaine, noribogaine, and other *iboga* alkaloids (40 mg/kg, i.p.) produces a significant decrease in dialysate DA in the NAC of *female* rats. Moreover, local infusion of high doses of ibogaine (100-400 μ M) through the dialysis probe reduces extracellular DA concentrations in the NAC of both male and female rats (69,70). Taken together, the *in vivo* neurochemical data indicate that systemic doses of ibogaine and noribogaine have minimal effects on dialysate DA in the NAC of male rats, but the same systemic doses produce significant decreases in dialysate DA in females. The pharmacokinetic data discussed previously can explain the heightened sensitivity of females to ibogaine. Because females have higher brain levels of ibogaine after systemic injection, the effects of the drug on DA neurons are enhanced and mimic the effects of local high-dose drug infusion.

The precise mechanisms responsible for the effects of ibogaine and noribogaine on DA neurons are not clear. Any hypothesis attempting to explain these effects must account for a number of contradictory pieces of information. For example, *iboga* alkaloids bind to DAT sites with low μ M affinity and block [3 H]DA reuptake *in vitro* (see Table III), yet these alkaloids do not uniformly elevate extracellular DA *in vivo* as measured by microdialysis. Such findings demonstrate a clear discrepancy between the *in vitro* and *in vivo* results. The available data from rats show that ibogaine-induced changes in central DA metabolism are not accompanied by elevations in extracellular DA levels *in vivo*. To complicate matters even more, there appear to be species differences in some dopaminergic actions of *iboga* alkaloids. Harsing *et al.* (71) reported that ibogaine stimulates release of preloaded [3 H]DA from mouse striata, while Wells *et al.* (60) showed that even high doses of ibogaine cause minimal [3 H]DA release from rat brain synaptosomes.

Staley *et al.* (21) have proposed that *iboga* alkaloids might promote a "reserpine-like" redistribution of intraneuronal DA from vesicular to cytoplasmic pools. While this hypothesis is purely speculative, there is evidence supporting the concept. Reserpine is known for its ability to disrupt the vesicular storage of monoamines, and the acute effects of ibogaine and noribogaine mimic the acute effects of reserpine on DA metabolism: all three drugs cause a depletion of tissue DA along with an increase in DOPAC and HVA (30,31,72). The effects of reserpine, however, are irreversible and long lasting, whereas the effects of *iboga*

alkaloids are reversible and transient. Ibogaine and noribogaine both display low μM potency at vesicular monoamine transporters (VMAT) labeled with [^{125}I]-tetrabenazine (21). These intracellular transporter sites are crucial for the accumulation of DA into synaptic vesicles. If *iboga* alkaloids interact with VMAT to disrupt compartmentalization of DA within vesicles, then stored DA would be redistributed into the cytoplasm. Under such circumstances, rapid metabolism of transmitter by monoamine oxidase would account for the dramatic decrease in tissue DA content and the parallel increase in acid metabolites.

Behavioral findings are consistent with the notion that *iboga* alkaloids might impair vesicular storage of DA, at least transiently. Sershen *et al.* (18) showed that acute ibogaine pretreatment (40 mg/kg, i.p., -2 hours) blocks the locomotor activity produced by cocaine, but not amphetamine, in mice. Similarly, Broderick *et al.* (68) reported that ibogaine reduces cocaine-stimulated locomotion in rats. More recently, Maisonneuve *et al.* (73) reported that pretreatment with either ibogaine or noribogaine (40 mg/kg, i.p., -1 hour) significantly attenuates the locomotor activity caused by cocaine administration in rats. It is well established that cocaine-induced psychomotor stimulant effects are dependent on a reserpine-sensitive vesicular pool of DA, whereas the effects of amphetamine are not (74). Thus *iboga* alkaloids appear reserpine-like in their ability to distinguish between two types of stimulants: DA reuptake blockers (i.e. cocaine) and DA releasers (i.e. amphetamine).

Glick and Maisonneuve (15) have proposed a neuronal circuit model that describes how ibogaine-induced changes in DA transmission might contribute to the antiaddictive properties of the drug. The neurochemical data reviewed above are consistent with the notion that dysregulation of normal DA function by *iboga* alkaloids renders DA neurons refractory to the effects of subsequently administered drugs of abuse. More studies are needed to unravel the complex mechanisms responsible for the dopaminergic actions of ibogaine and noribogaine.

B. EFFECTS ON SEROTONIN SYSTEMS

5-HT is an important neurotransmitter in mammals, and abnormalities in 5-HT function have been implicated in the etiology of psychiatric diseases including depression, obsessive-compulsive disorder, and schizophrenia (75,76). In rodent brain, neurons that synthesize and release 5-HT have their cell bodies located in the brain stem raphe nuclei. In particular, 5-HT cells of the dorsal and median raphe send axonal projections that ascend through the median forebrain bundle *en route* to terminal fields in all regions of the forebrain, including the PFC, NAC, and striatum. A number of studies have shown that pharmacological treatments causing increased synaptic 5-HT can suppress drug-seeking behavior in rodents trained to self-administer drugs of abuse (77,78). For instance, pretreatment with

the 5-HT selective reuptake inhibitor (SSRI), fluoxetine, decreases the self-administration of stimulants like cocaine and amphetamine (79,80). Similarly, the 5-HT releasing agent, fenfluramine, reduces the self-administration of methamphetamine and heroin (81,82). Other studies have shown that chronic exposure to alcohol and cocaine causes a 5-HT deficit syndrome that may contribute to the maintenance of a drug-dependent state (83-85). Thus, 5-HT neurons appear to have an important modulatory role in drug-seeking behavior and the development of drug addiction.

It seems reasonable to suspect that ibogaine exerts at least some of its effects via interaction with 5-HT neurons. The *iboga* alkaloids are chemically related to 5-HT since these alkaloids contain an indole moiety as part of their chemical structure (see Figure 1). In rodents, ibogaine administration causes tremors and forepaw treading (7-9,86), behaviors that are hallmark signs of the so-called "5-HT syndrome" initially described by Jacobs (87). While early radioligand binding studies indicated that ibogaine does not interact with 5-HT receptors *in vitro* (22,88), more recent data demonstrate that ibogaine displays low μM affinity ($\sim 5\text{-}10\ \mu\text{M}$) for 5-HT₂ receptor sites labeled with ketanserin (20,89). In support of the binding data, Helsley *et al.* (90,91, see Helsley *et al.* in this volume) used a drug discrimination paradigm in rats to show that stimulus properties of ibogaine are at least partially mimicked by 5-HT agonists with preferential affinity for 5-HT_{2A} and 5-HT_{2C} receptor subtypes. Collectively, such data suggest that ibogaine can act as a low potency 5-HT₂ agonist in rats. The role of 5-HT₂ sites in mediating the psychoactive properties of ibogaine in humans has not been evaluated, and this topic deserves further study.

Mash *et al.* (19) used radioligand binding methods to show that *iboga* alkaloids interact with SERT sites in the human occipital cortex. In their study, ibogaine and noribogaine displaced [¹²⁵I]RTI-55-labeled SERT binding with Ki values of 550 nM and 40 nM, respectively (see Table I). These data demonstrate that ibogaine and noribogaine exhibit much higher affinity for SERTs when compared to 5-HT receptor subtypes. Interestingly, Staley *et al.* (21) found that ibogaine and noribogaine are significantly more potent at SERT sites labeled with cocaine analogs (i.e., RTI-55) when compared to SERT sites labeled with SSRIs such as paroxetine. Thus, similar to the results from DAT binding studies, *iboga* alkaloids display selective affinity for a cocaine-binding site on SERT proteins. The significance of this finding is unknown but warrants investigation.

In order to evaluate the interaction of *iboga* alkaloids with SERTs in greater detail, the activity of ibogaine and noribogaine in assays measuring SERT binding and inhibition of [³H]5-HT uptake in rat brain tissue preparations was examined. As shown in Table III, ibogaine and noribogaine were observed to inhibit [¹²⁵I]RTI-55 binding to rat SERT sites with IC₅₀ values of 3.85 μM and 180 nM, respectively. While these IC₅₀ determinations are slightly higher than those observed in the human brain, all data agree that noribogaine has an approx-

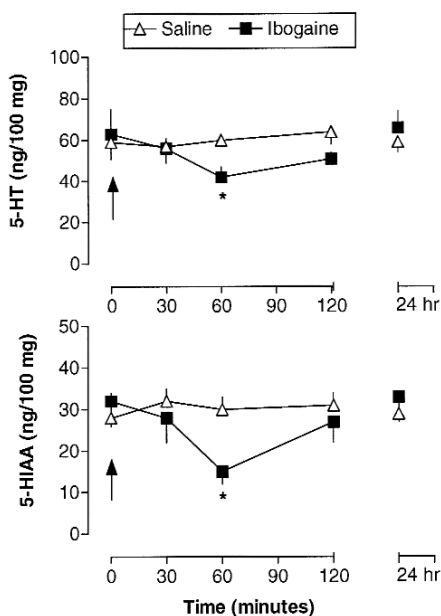


FIGURE 5. Time-course effects of ibogaine administration on postmortem tissue levels of 5-HT and 5-HIAA in rat caudate. Male rats received saline or ibogaine (50 mg/kg, i.p.) at time zero, and groups of rats (N = 6 per group at each time point) were sacrificed at various times thereafter. Tissue levels of 5-HT and 5-HIAA were assayed using HPLC-EC.

* = $P < 0.05$ compared to saline control at specific time points (31).

imately 10-fold greater affinity than ibogaine for binding to SERT. The data in Table III also show that ibogaine and noribogaine block [^3H]5-HT uptake in rat brain with IC_{50} values of 3.15 μM and 330 nM, respectively. These ibogaine results are consistent with the recent findings of Wells *et al.* (60), who reported that ibogaine inhibits [^3H]5-HT uptake in rat brain synaptosomes with an IC_{50} of 2.5 μM . These same investigators showed that ibogaine does not stimulate the release of preloaded [^3H]5-HT from nervous tissue; indeed, ibogaine antagonizes KCl-evoked release of [^3H]5-HT. Taken together, the findings indicate that ibogaine and noribogaine interact with SERT sites to inhibit 5-HT uptake and that noribogaine is 10 times more potent. Therefore, *iboga* alkaloids appear to affect 5-HT neurons *in vitro* in a manner similar to SSRIs.

A number of investigators have examined the effects of ibogaine on 5-HT neurotransmission in rodents (18,31,66-68). Most studies have used one of two methods to study 5-HT neurochemistry in whole animals: (1) measurement of 5-HT and its metabolite, 5-hydroxyindoleacetic acid (5-HIAA), in postmortem

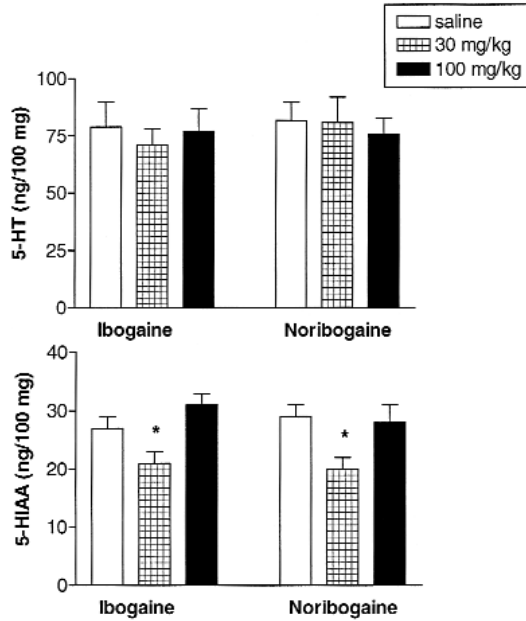


FIGURE 6. Dose-response effects of ibogaine and noribogaine on postmortem tissue levels of 5-HT and 5-HIAA in mouse caudate. Groups of male mice ($N = 6$ per group at each dose) received saline, ibogaine, or noribogaine and were sacrificed 60 minutes later. Tissue levels of 5-HT and 5-HIAA were determined using HPLC-EC.

* = $P < 0.05$ with respect to saline controls.

brain tissue, or (2) measurement of extracellular 5-HT in living brain via *in vivo* microdialysis. We assessed the time-course effects of ibogaine administration on postmortem tissue levels of 5-HT and 5-HIAA in dissected rat brain regions (31). Figure 5 shows that i.p. administration of ibogaine (50 mg/kg) produces an acute and transient reduction in tissue levels of 5-HIAA and 5-HT in rat caudate, with the decline in 5-HIAA being significantly more robust. In agreement with our data, Benwell *et al.* (66) showed that ibogaine decreases tissue levels of 5-HIAA in rat caudate and NAC. Thus, ibogaine produces a short-lived and modest reduction in 5-HT metabolism, as indicated by a decrease in the ratio of 5-HIAA/5-HT.

No published studies have assessed the effects of noribogaine on postmortem tissue levels of 5-HT and 5-HIAA. With this in mind, the effects of ibogaine and noribogaine on 5-HT metabolism in mouse caudate were compared. Figure 6 shows that administration of ibogaine or noribogaine, at a dose of 30 mg/kg i.p., significantly decreases 5-HIAA without affecting 5-HT. Curiously, this effect is

lost as the dose of either drug is increased to 100 mg/kg. Sershen *et al.* (18) demonstrated that i.p. administration of ibogaine to mice (40 mg/kg) produces a reduction in cortical tissue 5-HIAA that lasts for at least 24 hours after treatment. In general, the effects of *iboga* alkaloids on central 5-HT metabolism resemble the effects of SSRIs. Fluoxetine, for example, produces a consistent decrease in brain tissue 5-HIAA without affecting 5-HT (92). One notable exception to the fluoxetine-like effect of ibogaine is found in the medial PFC of rats. Benwell *et al.* (66) reported that ibogaine treatment (40 mg/kg, i.p.) causes a sustained increase in tissue 5-HIAA in the medial PFC that lasts for 7 days. More studies are needed to clarify the effects of acute ibogaine administration on 5-HT metabolism in discrete rat brain regions, especially in subdivisions of the cerebral cortex.

Broderick *et al.* (68) published the first study evaluating the effects of ibogaine on extracellular 5-HT *in vivo*. These investigators used *in vivo* microvoltammetry to show that ibogaine (40 mg/kg, i.p.) increases the concentration of extracellular 5-HT in rat NAC. We have used *in vivo* microdialysis methods to compare the effects of i.v. ibogaine and noribogaine on dialysate 5-HT levels in rat NAC (19,46). Our pharmacokinetic data show that metabolism of ibogaine to noribogaine is dramatically reduced when ibogaine is administered by the i.v. route (46). Thus, we used i.v. administration of ibogaine and noribogaine to assess the effects of the drugs without the complication of first-pass metabolism. In our experiments, indwelling jugular catheters and intracerebral guide cannulae aimed at the NAC were surgically implanted into anesthetized male rats. One week later, rats were subjected to microdialysis testing. Dialysate samples were collected at 20-minute intervals, and the dialysate concentrations of 5-HT were assayed using HPLC-EC. As depicted in Figure 7, i.v. injection of either ibogaine or noribogaine (1 and 10 mg/kg) causes a significant elevation in extracellular 5-HT in the NAC, and noribogaine is more potent in this regard. Ibogaine and noribogaine appear to display similar efficacy in their ability to increase dialysate 5-HT, since the maximal effect of both drugs is comparable (i.e., two- to threefold). The modest elevations in extracellular 5-HT produced by ibogaine and noribogaine are fully consistent with the ability of these drugs to bind to SERT sites and inhibit 5-HT reuptake.

In a recent publication, Wei *et al.* (93) reported that ibogaine and noribogaine produce large increases in dialysate 5-HT in the caudate and NAC of female rats. In their study, i.p. ibogaine (40 mg/kg) elicited a 20-fold increase in extracellular 5-HT in the NAC, whereas an equivalent dose of noribogaine caused an 8-fold increase. The authors concluded that ibogaine is a 5-HT releaser and noribogaine is a 5-HT uptake inhibitor. There are several caveats related to the findings of Wei *et al.* that deserve comment. First, the authors used female rats in their studies whereas other investigators have used males. The pharmacokinetic data described above show that females are more sensitive to the effects of ibogaine because of

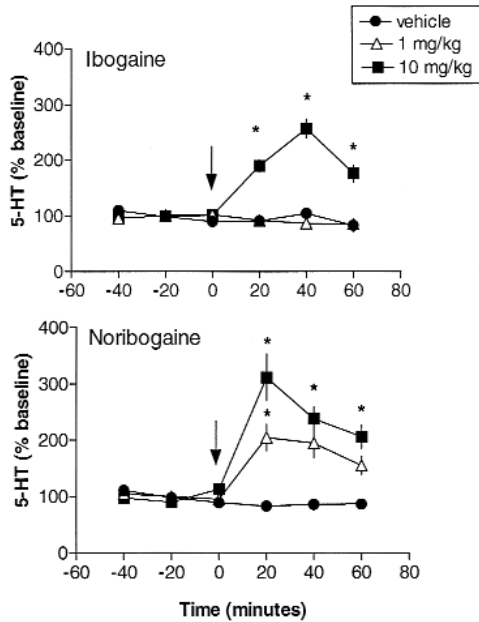


FIGURE 7. Dose-response effects of ibogaine and noribogaine on extracellular 5-HT in rat nucleus accumbens. After three baseline samples were collected, rats received i.v. injection of ibogaine, noribogaine, or ethanol:saline (10%) vehicle. Dialysate samples were collected at 20-minute intervals. Data are mean \pm SEM for N = 7 rats/group expressed as a percentage of preinjection baseline. Baseline concentration of dialysate 5-HT was 0.44 ± 0.08 nM.

* P < 0.05 relative to vehicle controls (46).

higher blood and brain levels of the drug, so data generated from female subjects must be interpreted cautiously. Second, only one dose of drug was tested in the Wei *et al.* study, precluding determination of dose-response effects. We (61), and others (94), have assessed the dose-response profiles of 5-HT-releasing agents and rarely observe such massive (i.e., 20-fold) elevations in extracellular 5-HT. Finally, the results of Wei *et al.* are difficult to reconcile with the *in vitro* findings of Wells *et al.* (60), who demonstrated that ibogaine does not release [3 H]5-HT from rat brain synaptosomes. One possible explanation for these discrepancies is that an unidentified metabolite of ibogaine is formed after i.p. injection, and this metabolite is a powerful 5-HT-releasing agent.

Based on the SERT binding data, [3 H]5-HT uptake data, and the bulk of the *in vivo* neurochemical data, we hypothesize that ibogaine and noribogaine are 5-HT reuptake inhibitors with a mechanism of action similar to fluoxetine (61,92,94). In addition, most evidence agrees that noribogaine is much more potent than

ibogaine as an indirect 5-HT agonist. A number of questions remain to be answered, however, with respect to the effects of *iboga* alkaloids on 5-HT neurons. For example, it seems peculiar that ibogaine and noribogaine display higher potency at SERT sites relative to DAT sites, yet the effects of the drugs on DA metabolism are more robust. Stated more simply, why do *iboga* alkaloids cause dramatic depletion of tissue DA, but not tissue 5-HT? Another important question relates to why *iboga* alkaloids do not uniformly decrease 5-HIAA/5-HT ratios in all regions of the brain. Further studies are needed to address these issues.

C. EFFECTS ON OPIOID SYSTEMS

Opioid drugs of abuse, such as heroin and morphine, elicit their effects by binding to opioid receptors located in nerve cell membranes. Historically, three subtypes of opioid receptors were identified on the basis of pharmacological data: mu-, delta-, and kappa-opioid receptor subtypes (95). Recent advances in molecular biology have demonstrated that mu, delta, and kappa receptors are derived from three separate genes (96). Moreover, all three opioid receptors and their gene transcripts are found in abundance within the mesolimbic neuronal circuitry implicated in drug-seeking behavior and drug dependence (97,98). It is well accepted that heroin and morphine are preferential mu-opioid receptor agonists, and activation of mu receptors is associated with the positive reinforcing effects (i.e., euphoria) of habit-forming opioids (99,100). Activation of kappa-opioid receptors, on the other hand, is associated with aversive effects (i.e., dysphoria). Interestingly, mu agonist administration increases extracellular levels of DA in the NAC whereas kappa agonists decrease extracellular DA in this region (101,102). Thus, mood and behavioral effects of opioids may be mediated, at least in part, via changes in DA transmission in the mesolimbic system.

Substantial evidence indicates that ibogaine modulates opioid transmission. For example, preclinical studies have shown that ibogaine can decrease morphine self-administration (7,9) and reduce opioid withdrawal symptoms (10,11). The opioid antagonist, naloxone, evokes a dramatic withdrawal syndrome when administered to morphine-dependent rats—the constellation of naloxone-precipitated symptoms includes grooming, burying, teeth-chattering, diarrhea, and wet-dog shakes. Ibogaine pretreatment reduces specific symptoms of naloxone-precipitated withdrawal in morphine-dependent rats, whether ibogaine is administered centrally (i.c.v.)(10) or peripherally (i.p.)(11). Experiments in mice have shown that ibogaine can decrease naloxone-precipitated withdrawal signs in this species as well (26,27). Clinical experience demonstrates that ibogaine administration alleviates the opioid withdrawal syndrome in human opioid addicts (12-14). Indeed, Lotsof (103) initially filed patents for ibogaine as a

pharmacotherapy for narcotics addiction (*Endabuse*) based on the ability of the drug to suppress opioid withdrawal symptoms in human heroin users. Alper *et al.* (13) recently collected data from a group of heroin addicts who received ibogaine treatment in nonmedical settings for the purpose of rapid opioid detoxification. In 25 of 33 patients, ibogaine eliminated opioid withdrawal symptoms, and this effect was sustained for 72 hours post-treatment. Finally, Mash *et al.* (104) have provided pharmacokinetic evidence suggesting noribogaine is responsible for the alleviation of opioid withdrawal in human patients treated with systemic ibogaine.

The fact that ibogaine suppresses opioid withdrawal symptoms in diverse animal species suggests that ibogaine and noribogaine might interact directly with opioid receptors. Early radioligand binding studies reported that ibogaine binds with low μM affinity ($\sim 2\mu\text{M}$) to kappa-opioid receptors, but is inactive at mu and delta sites (22). More recent work has demonstrated that ibogaine displays low μM potency at mu-opioid receptors labeled with [^3H]DAMGO and kappa-opioid receptors labeled with [^3H]U69,593 (20,23,24). Codd (105) examined the effects of ibogaine on [^3H]naloxone binding in mouse forebrain and resolved two ibogaine binding sites with K_i values of 130 nM and 4.0 μM . On the basis of sodium shift experiments, this investigator postulated that ibogaine is an opioid agonist that exhibits submicromolar affinity for mu-opioid receptors. Pearl *et al.* (23) published the first study directly comparing the potencies of ibogaine and noribogaine in opioid binding assays. Their findings showed that noribogaine displays higher affinity than ibogaine for mu- and kappa-opioid receptors. Additionally, noribogaine binds to delta-opioid sites with appreciable affinity ($\sim 20\ \mu\text{M}$), whereas ibogaine does not. We recently compared the ability of ibogaine and noribogaine to displace [^3H]DAMGO binding to mu-opioid receptors in rat thalamic membranes (24). The data demonstrate that ibogaine and noribogaine display affinities for the mu receptor of 3.76 μM and 160 nM, respectively. Other investigations have confirmed that noribogaine possesses much higher affinity for kappa-opioid sites when compared to ibogaine (21,27). In one study, Layer *et al.* (27) found that noribogaine is 10 to 100 times more potent than ibogaine at binding to kappa receptors, and this difference in potency is species dependent. Collectively, the radioligand binding results show that ibogaine and noribogaine bind to mu- and kappa-opioid receptors. Noribogaine is significantly more potent in this respect, with the drug exhibiting submicromolar affinities for mu and kappa subtypes under some binding conditions (see Table I).

It seems clear that *iboga* alkaloids can interact directly with opioid receptors, but traditional binding methods cannot provide information on drug efficacy (i.e., the degree to which a drug can elicit functional responses). Opioid receptors are linked to their intracellular transduction enzyme, adenylyl cyclase, via guanine nucleotide-binding proteins (G-proteins) (96). Agonist binding to an opioid receptor stimulates binding of GTP to G-proteins, thereby activating the G-

proteins and leading to a cellular response. Antagonist binding to an opioid receptor, in contrast, does not activate G-proteins and therefore does not lead to a cellular response. The findings of Codd (105) support the idea that *iboga* alkaloids might function as mu-opioid agonists. To assess the efficacy of ibogaine and noribogaine at mu-opioid receptors, we examined the effects of these drugs in the [³⁵S]GTPγS binding assay in rat thalamic membranes (24). In this assay, opioid agonists stimulate [³⁵S]GTPγS binding to G-proteins, whereas opioid antagonists do not. We observed that noribogaine stimulates [³⁵S]GTPγS binding in a naloxone-reversible manner with an EC₅₀ of 320 nM. Ibogaine, in contrast, is inactive in this assay at concentrations up to 100 μM. The intrinsic activity of noribogaine in the [³⁵S]GTPγS binding assay is comparable to the prototypical mu-opioid agonist DAMGO, suggesting noribogaine displays properties of a full-efficacy agonist at mu-opioid receptors.

The mu-opioid effects of noribogaine might explain the ability of systemically administered ibogaine to block opioid withdrawal. Theoretically, noribogaine could suppress opioid withdrawal by “substituting” for the addictive mu-opioid drug during acute abstinence. Indeed, mu-opioid agonist substitution-type medications, such as methadone and buprenorphine, are the most effective means of opioid detoxification (106). In addition, preliminary findings indicate that noribogaine binds to mu-opioid sites in a persistent manner, with dissociation rates in the range of days (107). Thus, noribogaine appears to display a unique profile of activity at mu-opioid receptors that includes low-affinity, pseudo-irreversible binding, and full-agonist efficacy. One caveat to the aforementioned hypothesis is that neither ibogaine nor noribogaine has significant analgesic potency *in vivo* (36,37). This finding is not consistent with the mu-opioid agonist actions of *iboga* alkaloids determined *in vitro*. On the other hand, noribogaine pretreatment is able to enhance the analgesic potency of morphine in rats and mice (36,37). The underlying basis for this peculiar finding is unknown, but it may be related to the purported ability of noribogaine to enhance mu-opioid receptor-mediated inhibition of adenylyl cyclase (108).

There is some data suggesting that the effects of ibogaine on DA neurons might be mediated by kappa-opioid receptors *in vivo*. As mentioned previously, local infusion of high-dose ibogaine (100 to 400 μM) into the NAC decreases extracellular levels of DA (69,70). Reid *et al.* (70) reported that reductions in dialysate DA levels produced by local infusion of ibogaine (100 μM) are reversed by coinfusion of the nonselective opioid antagonist naloxone (1 μM) or the kappa-opioid selective antagonist norbinaltorphine (1-10 μM). Glick *et al.* (109) reported comparable findings in female rats. These investigators showed that *i.p.* administration of norbinaltorphimine (10 mg/kg, *i.p.*) attenuates ibogaine-induced decreases in extracellular DA in the NAC. Few studies have examined the effects of receptor-selective opioid antagonists on the pharmacological actions of ibogaine and noribogaine *in vivo*, and more studies of this type need to

be carried out.

IV. Neuroendocrine Effects

Stress is a major factor contributing to the development of drug dependence (110,111). Studies in rats have shown that various types of stressors can facilitate acquisition of drug self-administration behavior (112-114) and trigger relapse during drug withdrawal (115,116). The effects of stress on drug-seeking behavior appear to be mediated by hormones of the hypothalamic-pituitary-adrenal (HPA) axis, particularly corticosterone (117,118). It is well known that corticosterone is secreted from the adrenal cortex in response to natural stressors or drugs of abuse. Corticosterone, in turn, can facilitate acquisition of drug self-administration

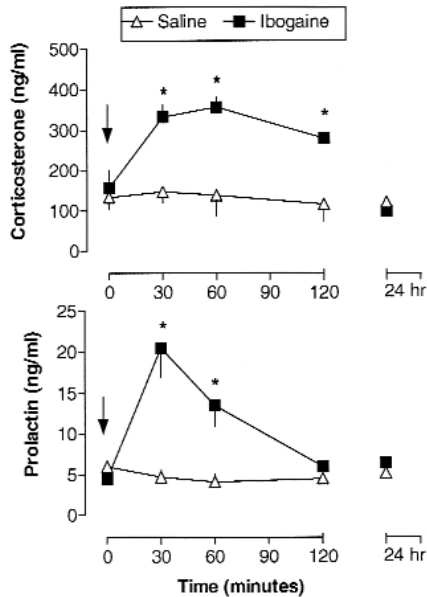


FIGURE 8. Time-course effects of ibogaine administration on circulating levels of corticosterone and prolactin in rats. Male rats received saline or ibogaine (50 mg/kg, i.p.) at time zero, and groups of rats (N = 6 per group at each time point) were sacrificed at various times thereafter. Plasma corticosterone and prolactin were assayed using radioimmunoassay (RIA) methods.

* = $P < 0.05$ compared to saline control at specific time points (31).

behavior, similar to the effects of stress (117,118). Reductions in circulating corticosterone, produced by surgical adrenalectomy or inhibition of corticosterone biosynthesis, decrease drug self-administration behavior (119,120). Interestingly, corticosterone itself appears to have intrinsic reinforcing properties because this hormone is readily self-administered under certain experimental conditions (121,122). Taken together, the preclinical data show that adrenal corticosteroids are important biological substrates mediating the ability of stress to influence the effects of abused drugs. Such findings may have clinical relevance, since drug addicts and clinicians alike would agree that stressful life events often contribute to relapse in human drug-dependent patients.

With reference to the preceding discussion, it seems pertinent to examine the neuroendocrine effects of *iboga* alkaloids. We have evaluated the time-course effects of ibogaine on the circulating levels of corticosterone and prolactin in rats (31,63,64). As discussed above, corticosterone is a major stress hormone of the

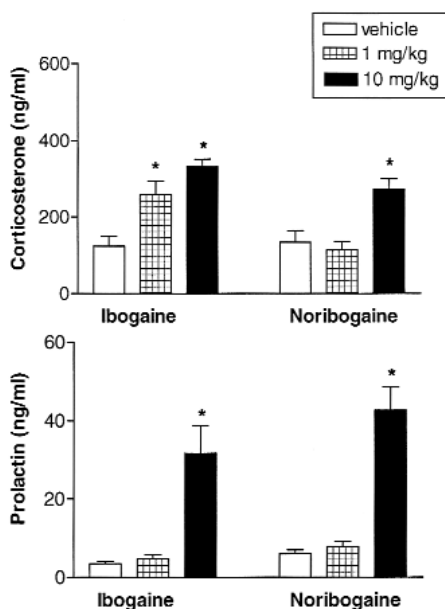


FIGURE 9. Dose-response effects of ibogaine and noribogaine on circulating corticosterone and prolactin in rats. Male rats bearing indwelling jugular catheters received i.v. injection of ibogaine, noribogaine, or ethanol:saline vehicle (10%), and blood samples were withdrawn via the catheters. Data are mean \pm SEM expressed as peak plasma hormone levels for N = 7 rats/group. Peak hormone secretion occurred at 30 minutes for corticosterone and at 15 minutes for prolactin.

* = $P < 0.05$ with respect to vehicle controls (46).

HPA axis. Prolactin is a protein hormone synthesized in the anterior pituitary that is also secreted in response to stress, but regulation of prolactin is independent of the HPA axis (123,124). The data in Figure 8 show that i.p. ibogaine administration (50 mg/kg) causes a sustained increase in corticosterone secretion that lasts for at least 2 hours. This effect is normalized within 24 hours. Ibogaine also elevates plasma prolactin, but this effect is short-lived, with hormone levels returning to baseline by 2 hours postinjection.

The effects of i.v. ibogaine and noribogaine on neuroendocrine secretion in rats were also compared. In these experiments, indwelling jugular catheters were surgically implanted into anesthetized male rats (46). After one week of recovery from surgery, rats received i.v. injection of ibogaine, noribogaine, or vehicle. Repeated blood samples were withdrawn via the catheters, and plasma was assayed for hormone levels by double-antibody RIA. Previous studies from our laboratory have shown that the chronic-catheterized rat model allows for repeated blood sampling with a minimum of stress to the animal (125).

As shown in Figure 9, plasma corticosterone levels are significantly increased after i.v. administration of ibogaine or noribogaine, but ibogaine is significantly more potent as a stimulator of the corticosterone secretion. After a 1 mg/kg dose, for instance, ibogaine elevates corticosterone whereas noribogaine does not. Ibogaine and noribogaine produce comparable increases in circulating prolactin that are seen only after the 10 mg/kg dose. The drug-induced hormonal effects reported here are likely to be mediated via central pathways because i.c.v. administration of ibogaine to rats causes elevations in circulating corticosterone and prolactin similar to those observed after i.p. and i.v. administration (Baumann, unpublished).

In our initial studies, we proposed that neuroendocrine effects of ibogaine might be mediated by central 5-HT neurons based on the similar *in vivo* effects of ibogaine and the 5-HT releaser, fenfluramine (31,63,125). However, the neurochemical data reviewed above suggest that 5-HT neurons are not involved in ibogaine-induced corticosterone secretion. The microdialysis data, for example, show that i.v. ibogaine is less potent than i.v. noribogaine in its ability to elevate extracellular 5-HT in the brain. Likewise, ibogaine has lower affinity for SERT and lower potency at blocking 5-HT uptake when compared to noribogaine. Thus, ibogaine is less potent as an indirect 5-HT agonist, but much more potent as a stimulator of corticosterone secretion. The mechanisms underlying the effects of *iboga* alkaloids on plasma corticosterone are unclear, and they could be mediated by any number of targets, including NMDA-coupled ion channels or sigma-2 receptors (see Table I). Similar to ibogaine, the noncompetitive NMDA antagonist, MK-801, is an activator of the HPA axis in rats (126). Ibogaine inhibits [³H]MK-801 binding in rat brain tissue and ibogaine mimics the electrophysiological, neuroprotective, and discriminative stimulus properties of MK-801 (25-27). Likewise, the prototypical sigma receptor drug phencyclidine

(PCP) elevates plasma corticosterone (127), and ibogaine displays submicromolar affinity for sigma-2 binding sites (16,17). It also seems possible that ibogaine-induced activation of the HPA axis may represent a nonspecific stress response secondary to the adverse behavioral consequences of ibogaine administration. Doses of ibogaine used in our studies cause tremors, forepaw treading, and ataxia (see below). Interestingly, noribogaine administration does not cause the same adverse behaviors as ibogaine, and noribogaine is less potent as an activator of the HPA axis in rats.

The mechanisms responsible for prolactin secretion elicited by ibogaine and noribogaine are not known, but may involve hypothalamic DA neurons (123). Under normal circumstances, secretion of pituitary prolactin is inhibited by tonic release of DA from tuberoinfundibular DA (TIDA) neurons in the mediobasal hypothalamus (128). TIDA nerve terminals in the median eminence release DA into the hypothalamic-hypophysial portal circulation in an endocrine fashion. DA, in turn, binds to DA D2 receptors on pituitary lactotrophs to directly inhibit prolactin secretion. The elevation of prolactin evoked by ibogaine and noribogaine might be mediated by a reduction in extracellular DA levels in the hypothalamus. Consistent with this proposal, ibogaine administration produces a significant decrease in tissue levels of DA in rat hypothalamus (63). However, no studies have examined the effects of *iboga* alkaloids on TIDA neuronal activity. It is noteworthy that mu- and kappa-opioid receptor agonists produce significant elevations in plasma prolactin, and this effect is mediated by suppression of DA release from TIDA neurons (129,130). Thus, the prolactin-releasing effect of ibogaine and noribogaine may involve activation of opioid receptors. No investigators have examined the ability of receptor antagonists to reverse the endocrine effects of ibogaine or noribogaine. Further studies are needed to determine the specific receptor sites involved in mediating the neuroendocrine actions of *iboga* alkaloids.

V. Adverse Consequences

A. BEHAVIORAL EFFECTS

Ibogaine is known to produce adverse behavioral effects in both humans and animals. In humans, oral administration of ibogaine (5 to 25 mg/kg) produces dizziness, nausea, vomiting, and motor incoordination that last for hours. Naranjo *et al.* (131,132) reported that ibogaine evokes a hallucinogenic-like visual experience that resembles a dream, but without loss of consciousness. The neurobiological underpinnings of the so-called waking dream state are not

known. In addition, the possible role of noribogaine in mediating specific aspects of the ibogaine-induced visual experience have not been studied. Some investigators have speculated that the psychoactive properties of ibogaine are important for the antiaddictive effects of the drug, and this hypothesis deserves to be investigated under controlled experimental conditions.

Administration of ibogaine to rats causes a spectrum of behaviors including tremors, forepaw treading, and ataxia (7-9,86). These motor behaviors are transient and resolve within the first few hours postinjection. Interestingly, the receptor mechanisms responsible for these ibogaine-induced behaviors have not been clarified. We have compared the effects of ibogaine and noribogaine on various motor behaviors in rats (46). As discussed previously, i.v. drug administration was used in these experiments because the i.v. route enables an assessment of drug-induced effects without the complication of significant first-pass metabolism. Rats received i.v. injection of ibogaine, noribogaine, or vehicle. Animals were observed for 90 second intervals at various times thereafter, and specific behaviors were scored using a graded scale: 0=absent, 1=equivocal, 2=present, 3=intense (46,125). Rats were given a single numerical score for each behavior that consisted of the summed total for that behavior across all time points.

The data in Figure 10 illustrate the effects of ibogaine and noribogaine on tremors and forepaw treading. Ibogaine produces a dose-related increase in the occurrence of tremors and forepaw treading; the ibogaine-induced tremorigenic effect consists of fine tremors of the face, head, and neck, as well as prominent shivering movements of the trunk. After the highest dose of ibogaine (10 mg/kg, i.v.), most rats display abnormal postures, body sway, and a staggering-type locomotion. In contrast to ibogaine, noribogaine does not elicit tremors or ataxia. Noribogaine does cause a slight stimulation of forepaw treading, but it is much less effective when compared to ibogaine. In addition, noribogaine increases the incidence of penile erections, a behavior that is rarely seen after ibogaine administration. It should be mentioned that behavioral effects elicited by both drugs are transient, with rats appearing completely normal by 30 minutes postinjection. Our findings with i.v. ibogaine are fully consistent with prior reports showing i.p. ibogaine elicits tremors and ataxia when administered to rats at typical antiaddictive doses (i.e., 40 mg/kg). In agreement with the i.v. noribogaine results, Glick *et al.* (35) demonstrated that i.p. noribogaine (40 mg/kg) is not tremorigenic when administered to female rats. Thus, ibogaine and noribogaine evoke quite different behavioral effects despite having similar chemical structures.

It might be assumed that ibogaine-induced actions are mediated by central 5-HT mechanisms because tremors and forepaw tapping are classic signs of the 5-HT behavioral syndrome (86,87,125). Irrespective of such similarities between the behavioral effects of ibogaine and certain 5-HT drugs (see 86), the data

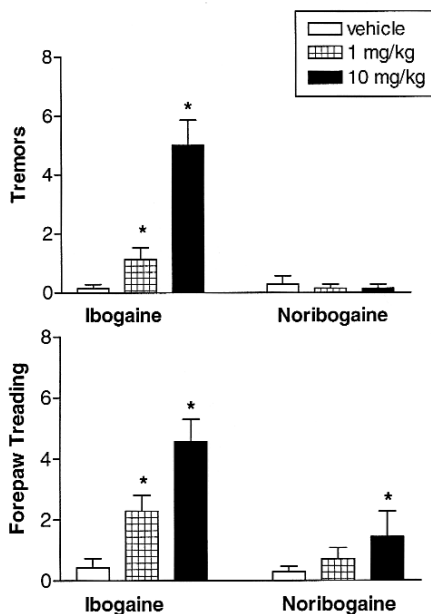


FIGURE 10. Dose-response effects of ibogaine and noribogaine on tremors and forepaw treading. Male rats bearing indwelling jugular catheters received i.v. injection of ibogaine, noribogaine, or ethanol:saline vehicle (10%). Behaviors were scored at 2, 10, 20, and 30 minutes postinjection. Rats were given a single numerical score that was the summed total for that behavior across all time points. Data are mean \pm SEM for N = 7 rats/group.

* = $P < 0.05$ with respect to vehicle controls (46).

discussed herein indicate that 5-HT mechanisms are probably not involved in the motor effects of ibogaine. Ibogaine is less potent than noribogaine as an indirect 5-HT agonist, yet ibogaine is more potent as a stimulator of tremors and forepaw treading. It is tempting to speculate that ibogaine-induced motor effects might involve NMDA-coupled ion channels or sigma-2 receptors. Ibogaine is significantly more potent than noribogaine at these sites (16,21,27, see Table I), possibly explaining why ibogaine evokes more potent behavioral actions. Similar to ibogaine, drugs that interact with sigma receptors (i.e., PCP) and NMDA sites (i.e., MK-801) are known to cause forepaw tapping and ataxia in rats (133,134). The mechanisms underlying ibogaine-induced tremor remain to be determined.

B. NEUROTOXICITY

Probably the most serious impediment to the development of ibogaine as an

antiaddictive medication is the reported neurotoxicity of the drug (135-137, see Molliver *et al.* in this volume). O'Hearn *et al.* (135,136) were the first to show that single or multiple injections of ibogaine (100 mg/kg, i.p.) cause glial cell proliferation and Purkinje cell degeneration in the rat cerebellar vermis. The effects of ibogaine in rat cerebellum are consistent with a trans-synaptic excitotoxic lesion that involves sustained activation of the olivocerebellar pathway (137). O'Callaghan *et al.* (138) examined the effects of ibogaine (100 mg/kg, i.p.) on tissue levels of glial fibrillary acidic protein (GFAP) in dissected rat brain regions. Increased expression of GFAP, a hallmark sign of astrogliosis, is a generic indicator of neuronal injury in the brain. These investigators demonstrated that ibogaine increases expression of GFAP in the cerebellum and in other brain areas such as the striatum and hippocampus. Somewhat surprisingly, Scallet *et al.* (139) reported that ibogaine-induced cerebellar injury is observed in rats, but not in mice. Sanchez-Ramos and Mash (140) found no evidence for neurotoxic damage in African green monkeys treated repeatedly with orally administered ibogaine (5 to 25 mg/kg). Thus, the neurotoxic effects of ibogaine appear to be species dependent, suggesting extrapolation of toxicity data across species lines is ill advised. No studies have systematically investigated the neurotoxic potential of noribogaine, and such studies need to be carried out.

The neurotoxic effects of ibogaine are clearly dose related. For example, Molinari *et al.* (141) demonstrated that a single injection of the typical antiaddictive dose of ibogaine (40 mg/kg, i.p.) does not cause cerebellar damage in female rats. Furthermore, repeated administration of lower doses of ibogaine (10 mg/kg, i.p.), given every other day for 60 days, does not affect Purkinje cell number in male rats (142). Recently, Xu *et al.* (143) evaluated the dose-response effects of single i.p. injections of ibogaine on markers of cerebellar neurotoxicity in rats. In their study, ibogaine doses of 75 and 100 mg/kg produced evidence for cerebellar damage in all rats tested. On the other hand, a dose of 25 mg/kg had no effect. An ibogaine dose of 50 mg/kg produced no obvious Purkinje cell degeneration, but it did increase cerebellar GFAP staining in one-third of the rats studied. Collectively, the neurotoxicity data show that the margin of safety for ibogaine administration in rats is very narrow, since therapeutic doses of the drug (i.e., 40 mg/kg, i.p.) are very close to the minimum doses required for eliciting cerebellar damage (i.e., 50 mg/kg, i.p.).

The mechanism underlying ibogaine-evoked neurotoxicity is not known. Vilner *et al.* (144, 145) have provided evidence that sigma-2 receptors might be involved in the neurotoxic effects of ibogaine (see Bowen *et al.* in this volume). These investigators examined sigma-2 receptor-mediated cytotoxicity in human SK-N-SH neuroblastoma cells cultured *in vitro*. Incubation of neuroblastoma cells with sigma-2 drugs, including ibogaine, causes dose- and time-dependent morphological changes that are characterized by loss of processes, detachment, and ultimately cell death. The same sigma-2 ligands produce elevations in

intracellular Ca^{++} concentrations in neuroblastoma cells that may be causally linked to cytotoxicity. Interestingly, noribogaine is not toxic to neuroblastoma cells in culture, consistent with the lack of affinity of noribogaine for sigma-2 receptors (16, Table I). The exact relationship between sigma-2 cytotoxicity *in vitro* and ibogaine-induced cerebellar degeneration *in vivo* remains to be established. One caveat to the sigma-2 receptor hypothesis of ibogaine neurotoxicity relates to the effects of the beta-carboline compound, harmaline. Harmaline causes cerebellar neurotoxicity in rats analogous to the effects of ibogaine (135-137), but harmaline has little affinity for sigma-2 binding sites (16). More studies are needed to determine the precise mechanisms responsible for the neurotoxic effects of *iboga* alkaloids. In particular, direct comparisons of the neurotoxic potential of ibogaine, noribogaine, and other *iboga* alkaloids need to be carried out.

VII. Conclusions

The data reviewed in this chapter show that ibogaine interacts with multiple neurotransmitter systems known to modulate drug addiction (see Table I). The *in vivo* pharmacological activity of ibogaine is further complicated by the metabolic conversion of ibogaine to its active *O*-desmethyl metabolite, noribogaine, in rats, monkeys, and humans (19,21,29,34,41,46). After ibogaine administration to rats (40 mg/kg, i.p.), concentrations of noribogaine in blood and brain tissue are equal to, or exceed, the levels of ibogaine itself. Moreover, noribogaine has a much longer biological half-life than ibogaine, with pharmacologically relevant concentrations of noribogaine persisting in the bloodstream for at least one day after ibogaine treatment. These findings suggest the possibility that noribogaine contributes to the antiaddictive properties of systemically administered ibogaine. Moreover, noribogaine might be the active compound mediating the long-term actions of ibogaine. Indeed, Glick *et al.* (35) have shown that ibogaine and noribogaine are equipotent in their ability to produce long-lasting reductions in the self-administration of cocaine and morphine in rats.

Gender and gonadal steroid hormones can influence ibogaine pharmacokinetics and metabolism in rats and possibly other species (29). When ibogaine is administered to female rats during the preovulatory phase of the reproductive cycle (i.e., high estrogen levels), concentrations of ibogaine in blood and brain tissue are much higher than those of similarly treated males (see Table II). We speculate that elevated levels of circulating estrogen enhance the absorption of ibogaine from peripheral compartments into the bloodstream. Such gender-dependent alterations in ibogaine pharmacokinetics may serve to explain the

heightened sensitivity of female rats to the neurochemical, behavioral, and neurotoxic effects of ibogaine (29,138).

Perhaps the most dramatic neurochemical effects produced by *iboga* alkaloids are on DA metabolism in the brain. Ibogaine and noribogaine are equipotent in their ability to evoke a transient stimulation of DA metabolism that is characterized by profound depletion of tissue DA (~50% reduction) in mesolimbic, mesocortical, and mesostriatal terminal projection areas (18,30,31,63-65). The reserpine-like depletion of DA is short-lived, but this effect could have long-term consequences. For example, dysregulation of DA function produced by ibogaine and noribogaine may alter the responsiveness of DA neurons to the effects of subsequently administered drugs of abuse. Consistent with this notion, ibogaine pretreatment can block the drug-induced elevations in extracellular DA in rat NAC normally produced by cocaine, morphine, and nicotine (66-68). Thus, alterations in DA transmission may represent a common mechanism underlying the ability of *iboga* alkaloids to suppress the self-administration of diverse types of addictive drugs.

Ibogaine and noribogaine bind to SERT sites and inhibit 5-HT uptake *in vitro*; noribogaine is at least 10 times more potent than ibogaine in this regard (19,21, see Table III). The blockade of 5-HT uptake afforded by ibogaine and noribogaine leads to elevations in extracellular 5-HT in the NAC *in vivo*. The serotonergic actions of *iboga* alkaloids resemble the actions of SSRIs such as fluoxetine. It seems plausible that fluoxetine-like effects of ibogaine, and especially noribogaine, might contribute to the antiaddictive properties of systemically administered ibogaine. Elevations in synaptic 5-HT could help to prevent relapse by alleviating withdrawal-associated depression, reducing drug craving, and decreasing the impulse to use drugs (146-148). In addition, elevations in synaptic 5-HT may enhance the mu-opioid activity of noribogaine, similar to the dual mechanism of action of the novel opioid, tramadol (149,150). Such 5-HT-opioid synergism could contribute to the ibogaine-induced suppression of opioid withdrawal symptoms that has been observed in heroin-dependent subjects.

Emerging evidence shows that ibogaine and noribogaine interact with opioid receptors in the brain, and noribogaine has much higher affinity at mu-, delta-, and kappa-opioid receptor subtypes (21-24,27). Recent findings suggest that noribogaine displays a unique profile of activity at mu-opioid receptors including low affinity, persistent binding, and full agonist efficacy. Thus, noribogaine may function as a methadone-like substitution medication that attenuates opioid withdrawal symptoms via direct agonist actions at mu-opioid receptors. The possible role of delta- and kappa-opioid receptors in mediating the antiaddictive properties of ibogaine and noribogaine is largely unexplored. It is noteworthy that kappa opioid agonists have been considered as potential pharmacotherapies for stimulant addiction based on a growing body of preclinical literature (151,152).

The collective findings suggest that noribogaine might be superior to ibogaine as an antiaddictive medication, due to the higher affinity of noribogaine at SERT sites and multiple opioid receptor subtypes. In addition, noribogaine appears to exhibit a superior side-effects profile when compared to ibogaine. Ibogaine causes tremors and ataxia in rats, whereas noribogaine does not. Possibly because noribogaine does not produce adverse behavioral effects, noribogaine is less potent as a stimulator of the HPA axis. A lack of sigma-2 receptor activity may render noribogaine free from the cerebellar toxicity associated with ibogaine. Thus, based on the data reviewed in this chapter, we propose that noribogaine may be a more effective and safer alternative to ibogaine as a candidate for medication development. Future studies should examine the antiaddictive potential of ibogaine and noribogaine in drug-dependent human patients under well-controlled experimental conditions.

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